UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: December 12, 2017

SUBJECT: Streptomycin. Human Health Risk Assessment to Support the Section 3 Registration and Establishment of New Tolerances on Tomato and Grapefruit, and a Crop Group Conversion to Pome Fruit Group 11-10.

PC Code: 006310 (sulfate salt) and 006306
Decision No.: 486865
Petition No.: 4E8236
Risk Assessment Type: Single chemical/aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D418018
Registration No.: 80990-4
Regulatory Action: Section 3
Case No.: NA
CAS No.: 3810-74-0 (sulfate salt) and 57-92-1
40 CFR: 180.245

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1.0 Executive Summary

Streptomycin is an antibiotic of the aminoglycoside class and is produced by the bacteria *Streptomyces*. The aminoglycosides are so named because they consist of several sugars with glycosidic bonds and contain amino groups. Streptomycin is registered for use on vegetable, fruit tree, and row crops, as well as garden and ornamental uses. The Interregional Research Project Number 4 (IR-4) has submitted field trial data and processing studies to support the use of a 17% wettable powder (WP) formulation of streptomycin sulfate (Firewall™ 17 WP) on grapefruit and tomato. Also, crop group conversion of the Pome Fruit Group 11 to Pome Fruit Group 11-10 was proposed.

Hazard Characterization: There are no guideline toxicity studies for streptomycin, and all toxicological data requirements were waived because of the extensive database from drug use of streptomycin in humans and animals. The toxicity of streptomycin was assessed using toxicity reviews provided by the Food and Drug Administration (FDA) and from the published literature on drug use. Streptomycin is an injectable antibiotic, which acts by interfering with protein synthesis. It has been used in humans and animals for the last 70 years. When used as a human drug, streptomycin is given by injection because it is very poorly absorbed by the oral route. Streptomycin injections can cause inner ear toxicity resulting in vestibular problems with loss of balance or equilibrium; hearing loss; and mild, reversible kidney toxicity.

The endpoint for chronic dietary, incidental oral, and inhalation exposures is based on decreased body weight in a 2-year rat feeding study submitted to the FDA. This endpoint is considered protective of toxicity reported in humans. No toxicity from acute exposure was identified, and an acute toxicity endpoint was not selected. Because oral absorption of aminoglycosides related to streptomycin is less than 1%, and because the skin has a protective barrier role compared to the lining of the GI tract, dermal absorption should be much less than that by the oral route; and toxicity by the dermal route at environmental concentrations is not expected. Therefore, quantitation of risk following dermal exposure was not required. Streptomycin injections have been used for many years to treat pregnant women. Children born to mothers treated with streptomycin injections have sometimes had hearing loss; no teratogenic effects have been attributed to streptomycin treatment. Because the doses selected for risk assessment are much lower than the injected dose at which toxicity occurs in humans, and at the levels of exposure anticipated due to pesticidal uses, there is no indication of neurotoxicity or susceptibility, and there are no residual concerns in the exposure database, the Food Quality Protection Act (FQPA) safety factor is reduced to 1x.

Residue Chemistry and Dietary Assessment: The residue of concern for tolerance and risk assessment purposes is parent streptomycin. The grapefruit and tomato (field and greenhouse) field trials and processing studies are considered scientifically acceptable and are supported by adequate storage stability data and analytical methods. An unrefined chronic dietary exposure and risk analysis was conducted using tolerance-level residues for all the registered and proposed new uses, 100% crop treated assumptions for all crops, default processing factors for all processed commodities except grapefruit juice and tomato puree, and tolerances established for livestock commodities resulting from uses as an animal drug. The estimated exposure (food and drinking water) to the U.S. population from the existing and proposed new uses of streptomycin

resulted in an estimated risk equivalent to 41% of the chronic population adjusted dose (cPAD). The most highly exposed subpopulation was all infants (<1 year old) with an estimated exposure equivalent to 91% of the cPAD.

Residential Risk Assessment: The existing residential uses on residential ornamental gardens and trees were previously assessed, and there were no residential handler inhalation risk estimates of concern. Residential handler and post-application dermal exposure assessments were not conducted for treated gardens and trees because there is no dermal hazard identified for streptomycin. Furthermore, non-dietary ingestion and inhalation post-application exposure following treatment of ornamentals is assumed to be negligible.

Non-Occupational Spray Drift Assessment: A quantitative assessment of exposure and risk resulting from spray drift has been conducted for streptomycin in a recent exposure and risk assessment, which resulted in no incidental oral risk estimates of concern for children (1 < 2 year old) [i.e., all margins of exposure (MOEs) ≥ 100] at the field edge for the maximum registered agricultural rate of 0.5 lb streptomycin/A for airblast applications. Since the rate assessed previously for spray drift resulting from airblast applications is higher than the proposed rate, this previous assessment is protective of the proposed Section 3 use.

Occupational Risk Assessment: Occupational handler exposure (inhalation only) was assessed for the proposed uses of streptomycin. All occupational handler MOEs are greater than the LOC of 100 with label-required personal protective equipment (PPE; use of a dust/mist respirator) and are thus not of concern. As there is no dermal hazard for streptomycin, quantification of occupational handler and post-application dermal exposure/risk is not required. Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for streptomycin at this time. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment.

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. Additional information on how these studies are considered can be found in Appendix D.

2.0 HED Recommendations

Provided revised Sections B and F are submitted, there are no hazard, residue chemistry, or occupational/residential considerations that would preclude granting the requested registrations and establishing the recommended tolerances for streptomycin in/on tomato and grapefruit, and the crop group conversion to Pome Fruit Crop Group 11-10. The specific tolerance and label recommendations are discussed in Sections 2.2 and 2.3, respectively.

2.1 Data Deficiencies

The proposed tolerance enforcement method is considered acceptable; however, another transition or alternate method is needed to confirm the identity of streptomycin.

Analytical standards for streptomycin are not available at the EPA National Pesticide Standards Repository and need to be sent to the repository. A reference standard for streptomycin must be provided to the Repository, and then replenished as requested by the Repository. The reference standard should be sent to the Analytical Chemistry Lab, which is located at Fort Meade, to the attention of Theresa Cole at the following address:

USEPA
National Pesticide Standards Repository/Analytical Chemistry Branch/OPP
701 Mapes Road
Fort George G. Meade, MD 20755-5350

The full 9 digit zip code is mandatory or the mail will be returned.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

A new tolerance enforcement method is available for enforcement of tolerances of streptomycin on tomato and grapefruit. Streptomycin residues are extracted from grapefruit fruit and dried pulp and tomato paste using potassium phosphate buffer containing pectinase and cellulase. The extract is filtered and cleaned-up with a C_8-solid-phase extraction cartridge. The pH of the eluate was adjusted to pH 8 and further cleaned with a weak cation exchange solid-phase extraction cartridge. The methanolic eluates are then evaporated and reconstituted in water. The reconstituted residues are then analyzed by ion-pair reversed-phase liquid chromatography with detection by MS/MS spectrometry. The Limit of quantitation (LOQ) has been demonstrated to be approximately 0.01 ppm.

2.2.2 Recommended Tolerances

The tolerances recommended for new and existing uses of streptomycin are included in Table 2.2.2. HED recommends updating the tolerance expression and consolidating permanent tolerances under a single section.

Table 2.2.2. Tolerance Summary for Streptomycin.

Commodity	Proposed*/Established Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments (*correct commodity definition*)
Section (a)(1)			
Grapefruit	0.15*	0.15	
Grapefruit, dried pulp	0.63*	0.30	
Tomato	0.5*	0.50	
Tomato, paste		1.2	
Fruit, pome, group 11	0.25	Remove	
Fruit, pome, group 11-10	0.25*	0.25	
Celery		0.25	
Pepper		0.25	
Potato		0.25	
Section (a)(2)			
Celery	0.25	Remove	

Table 2.2.2. Tolerance Summary for Streptomycin.			
Commodity	**Proposed*/Established Tolerance (ppm)**	**HED-Recommended Tolerance (ppm)**	**Comments (*correct commodity definition*)**
Pepper	0.25	Remove	
Tomato	0.25	Remove	
Section (a)(3)			
Potato	0.25	Remove	
Section (b)			
Grapefruit	0.15	Remove	
Grapefruit, dried fruit	0.40	Remove	

Currently, the 40 CFR 180.245 has three subsections under (a), two of these, (2) and (3), specify the type of treatment. This information is not considered necessary. In addition, time-limited tolerances for grapefruit commodities are not necessary. Therefore, HED recommends modification and simplification of the 40 CFR 180.245 by:

- Removal of the celery, pepper, and tomato tolerances listed under (a)(2), and the potato tolerance listed under (a)(3);
- Establishment of the 0.25 ppm tolerances for tomato, celery, pepper, and potato under (a)(1);
- Removal of the existing time limited tolerances for grapefruit and grapefruit, dried pulp listed under section (b) upon establishment of the permanent tolerances of 0.80 ppm for fruit, citrus, group 10-10 and 3.0 ppm for citrus, dried pulp.

Finally, the tolerance expressions under sections (a)(2), (a)(3) and (b) should be removed and the tolerance expression under (a)(1) should be modified according to the Interim Guidance on Tolerance Expressions (S. Knizner, 05/27/2009) to read as follows:

(a) General. Tolerances are established for residues of the fungicide streptomycin, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only streptomycin (*N,N'''-[(R,2R,3S,4R,5R,6S)-4-[[5-deoxy-2-O-[2-deoxy-2-(methylamino)-α-L-glucopyranosyl]-3-C-formyl-α-L-lyxofuranosyl]oxy]-2,5,6-trihydroxy-1,3-cyclohexanediyl]bis[guanidine]*) in or on the commodity.

2.2.3 Revisions to Petitioned-For Tolerances

A tolerance of 1.2 ppm is recommended for tomato paste. A tolerance for this commodity was not recommended by the petitioner, but is needed based on the results of the tomato processing study. A tolerance of 0.30 ppm is recommended for grapefruit dried fruit. The tolerance recommended by the petitioner is based on the use of the grapefruit tolerance instead of the highest average field trial (HAFT) residue. HED uses the HAFT to estimate tolerances for processed commodities.

2.2.4 International Harmonization

There are no established Codex or Canadian Maximum Residue Levels (MRLs) for streptomycin (Appendix C); therefore, there are no issues of harmonization.

2.3 Label Recommendations

2.3.1 Recommendations from Residue Reviews

Tomato: The label includes a table with instructions to prepare solutions with a variety of concentrations. The concentrations in this table are based on streptomycin; however, the column indicates that these are based on the active ingredient (which would be streptomycin sulfate). This table needs to be clarified to indicate that the concentrations are based on streptomycin. Alternatively, the table may be changed to express concentrations in terms of streptomycin sulfate. For tomato seedlings grown in greenhouse, a PHI of 1-day needs to be specified, and the maximum number of applications supported by residue data is four, which results in a maximum seasonal rate of 4.4 lbs Firewall/A. This maximum seasonal application rate needs to be specified on the label. For tomato transplants in the field or greenhouse, the maximum seasonal rate needs to be specified per acre, e.g. 4 lbs. FireWall 17 WP/A/season. Because tomato may be rotated to other crops, a plant back interval of 60-days is recommended to support the use of streptomycin on tomato.

Grapefruit: The crop field trial was conducted following a single application rate of 2 lbs Firewall/A (i.e., 0.44 lbs ai/A or 0.34 lbs streptomycin/A). The label needs to be modified to specify this maximum single application rate.

2.3.2 Recommendations from Occupational Assessment

There are no label recommendation resulting from the occupational risk assessment.

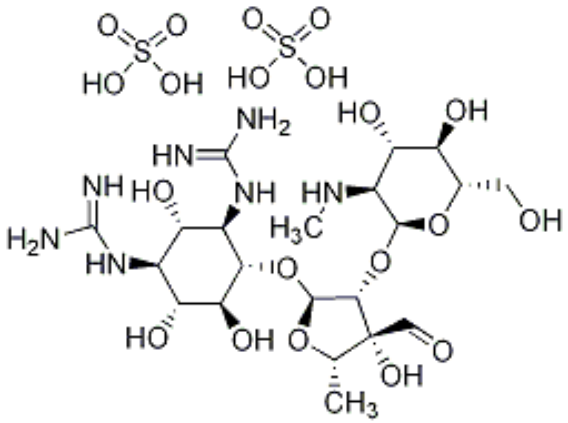
2.3.3 Recommendations from Residential Assessment

There are no label recommendation resulting from the residential risk assessment.

3.0 Introduction

Streptomycin is an antibiotic of the aminoglycoside class and is produced by the bacteria, *Streptomyces*. The aminoglycosides are so named because they consist of several sugars with glycosidic bonds and contain amino groups. Streptomycin was the first aminoglycoside antibiotic to be discovered in 1943 and has seen widespread use as an injectable drug since that time. The active ingredient evaluated is streptomycin sulfate, which dissociates in water to yield streptomycin. Therefore, both the risk assessment and the tolerance expression include the residues of streptomycin only.

3.1 Chemical Identity

Table 3.1. Test Compound Nomenclature.	
Chemical Structure	
Common Name	Streptomycin Sulfate
IUPAC Name	1,1-{1-L-(1,3,5/2,4,6)-4-[5-deoxy-2-O-(2-deoxy-2-methylamino-α-L-glucopyranosyl)-3-C-formyl-α-L-lyxofuranosyloxy]-2,5,6-trihydroxycyclohex-1,3-ylene}diguanidine
PC Code	006310
Chemical Abstracts No.	3810-74-0
Registration Review Case No.	0169
Chemical Class	Antibiotic

3.2 Physical/Chemical Characteristics

Technical streptomycin is a light tan solid with a melting point of 168 °C. Streptomycin is miscible with methanol, ethanol, isopropanol, carbon tetrachloride, and ether. It has a water solubility of more than 20 mg/mL at 28 °C. Additional physicochemical properties can be found in Table 3.2.

Table 3.2. Physicochemical Properties of the Streptomycin		
Parameter	**Value**	**Reference**
Molecular weight (g/mole)	1467.48 (sulfate salt)	D176743, 6/19/92, C. Swartz
Melting point/range (°C)	168 °C	D176743, 6/19/92, C. Swartz
pH	5.5 (1g sample/ 5 mL water)	D176743, 6/19/92, C. Swartz
Density (g/cm^3)	1.78	D176743, 6/19/92, C. Swartz
Water solubility (at 28°C)	>20 mg/mL	*Merck* 12, 8983
Solvent solubility	Soluble in methanol, ethanol, isopropanol, carbon tetrachloride, and ether	*Merck* 12, 8983
Dissociation constant (pK_a)	7.97	D187344, 5/4/93, C. Swartz
Octanol/water partition coefficient Log(K_{OW})	Waived	

3.3 Pesticide Use Pattern

The proposed use pattern for Firewall 17 WP end-use product is presented in Table 3.3. The application rates are presented in terms of lbs product per acre, lbs ai per acre (where the active

ingredient (ai) is streptomycin sulfate) and lb streptomycin/A. Note that in this document the application rates are also expressed as lbs streptomycin per acre (lbs strep/A) because the application rates used for the crop field trials were reported in terms of streptomycin *per se*.

Table 3.3. Summary of Proposed Directions for Use of Streptomycin.

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate[1]	Max. No. Applic. per Season	Max. Seasonal Applic. Rate	PHI (days)	Use Directions and Limitations
Grapefruit						
Foliar Spray	17% WP [80990-4]	1.5 – 3 lbs (0.34 - 0.67 lbs ai) per acre	NS	NS	60	21-day RTI; spray near runoff. Do not apply more than 4 lbs 17 WP per acre per season. For young trees, spray with 400 ppm concentration.
Tomato (seedlings in greenhouse)						
Foliar Spray	17% WP [80990-4]	(4 oz/25 gal) 0.056 lbs ai applied to 10,000 ft^2	6	NS	NS	4-day RTI. Apply first spray when seedlings are at 2-leaf stage, when first true leaves appear.
Tomato (transplants in field or greenhouse)						
Foliar Spray	17% WP [80990-4]	1 lb. (0.22 lbs ai) /A	NS	4 lbs FireWall per season	1	7-day RTI; Apply as foliar spray to near runoff.

NS = Not specified.

[1] The application rates are in term of streptomycin sulfate. The maximum single application rates of 1 lbs FireWall/A, 0.056 lbs ai/10,000 ft^2, and 3 lbs of FireWall/A correspond to rates of 0.17 lbs strep/A, 0.043 lbs strep/A, and 0.51 lbs strep/A (based on parent streptomycin).

Conclusions. Although the tomato field trials show a wide range of single and maximum application rates, generally, the average single rate and maximum seasonal rate used correspond to application rates of 1.2 lbs product/A (i.e., 0.26 lbs ai/A or 0.20 lbs strep/A) and 4.7 lbs product/A (i.e. 1 lb ai/A or 0.80 lbs strep/A). The label specifies single and maximum seasonal rates of 1 lb product/A (0.22 lbs ai/A), and 4 lbs product/A. The crop field trial data support these application rates. The following label clarifications are recommended: (1) The label includes a table with instructions to prepare a solution with a variety of concentrations, e.g. 200 ppm prepared by mixing 4 oz of 17 WP in 25 gallons of water. The concentrations in this table are based on streptomycin; however, the column indicates that these are based on the active ingredient. This table needs to be clarified to indicate that the concentrations are based on streptomycin. Alternatively, the concentrations in the label can be expressed in terms of streptomycin sulfate. Because the crop field trials were performed with 200 ppm of parent streptomycin, we recommend that this concentration is specified on the label under the instructions for uses on tomato with a range of recommended spray volumes. (2) For tomato seedlings grown in greenhouse, a PHI of 1-day needs to be specified, and the maximum number of applications (at the single rate of 0.056 lbs ai/10,000 ft^2) supported by residue data is four, which results in a maximum seasonal rate of 4.4 lbs prod/A. The maximum seasonal application rate needs to be specified in the label. (3) The crop field trial and greenhouse residue data supports the labeled maximum seasonal rate of 4 lbs prod/A for transplants in the field or greenhouse (note a typo in the proposed label, the rate needs to be specified per acre, e.g. 4 lbs.

Firewall 17 WP/A/season). (4) Since tomato may be rotated to other crops, the establishment of an interim rotational crop restriction of 60-days in the proposed label is required.

The grapefruit field trials were conducted following two applications at 0.340-0.350 lb strep/A/application (~ 2 lbs prod/A) with 20-21 day retreatment intervals for total seasonal rates of 0.681-0.693 lb strep/A (~ 4 lbs prod/A). This information does not support the labeled single application rate of 3 lbs prod/A (i.e. 0.68 lbs ai/A) for mature trees. Based on this, the label needs to be modified to specify a maximum single application rate of 2 lbs prod/A (0.44 lbs ai/A).

3.4 Anticipated Exposure Pathways

Humans may be exposed to streptomycin from the existing and proposed uses in food and drinking water, since streptomycin may be applied directly to growing crops and application may result in streptomycin reaching surface and ground water sources of drinking water. Residential uses of streptomycin on ornamentals may result in exposure in residential settings. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. There is a potential for post-application exposure for workers re-entering treated fields. There is also the potential for non-occupational exposure in residential areas to streptomycin resulting from spray drift from agricultural applications.

Risk assessments have been previously prepared for the existing uses of streptomycin. This risk assessment considers all of the aforementioned exposure pathways based on the proposed new uses of streptomycin, but also considers the existing uses as well, particularly for the dietary exposure assessment.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (https://www.epa.gov/laws-regulations/summary-executive-order-12898-federal-actions-address-environmental-justice). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the United States Department of Agriculture (USDA) under the National Health and Nutrition Survey/What We Eat in America (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the

development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

The most comprehensive risk assessment for streptomycin is in the 1992 Re-registration Eligibility Decision (9/30/1992). No new toxicity and/or metabolism data have been received since the last risk assessment. This assessment includes summaries of prior assessments (K. Farwell; D394862, 07/23/2012 and D310387, 08/04/2005).

4.1 Toxicology Studies Available for Analysis

There are no guideline toxicity studies available to assess pesticidal uses of streptomycin. The toxicity of streptomycin was assessed using the extensive published literature on drug use of streptomycin in humans and in animals, as well as with several toxicity summaries provided by the FDA.

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

Following intramuscular injection of 1 gram of streptomycin as the sulfate, a peak serum level of 25-50 µg/mL is reached within 1 hour, diminishing slowly to about 50% after 5 or 6 hours. Appreciable concentrations are found in all tissues except the brain. Significant amounts have been found in pleural fluid and tuberculous cavities. Streptomycin passes through the placenta with serum levels in the cord blood similar to maternal levels. Small amounts are excreted in milk, saliva, and sweat. Streptomycin is excreted by glomerular filtration. In patients with normal kidney function, between 29% and 89% of a single 600 mg dose is excreted in urine within 24 hours[1]. Streptomycin is very poorly absorbed by the oral or dermal routes, and because of this, drug treatment is by intramuscular injection.

4.3 Toxicological Effects

Injections of streptomycin as a drug (up to a gram), at doses much higher than expected from dietary or residential routes of exposure to pesticidal uses, can cause inner ear toxicity resulting in vestibular problems with loss of balance or equilibrium. Injections also sometimes cause hearing loss and mild, reversible kidney toxicity. Children born to mothers treated with streptomycin injections have sometimes had hearing loss. No teratogenic effects were noted in a non-guideline rabbit developmental study. In a non-guideline 2-year rat feeding study, the only adverse effect noted was reduced body weight in males; an increase in treatment-related tumors was not reported. The acute oral toxicity for streptomycin is very low; the LD_{50} was 9,000 mg/kg in both rats and mice.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

[1] http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/064210s009lbl.pdf

No teratogenic effects were noted in a rabbit developmental study at the high dose of 10 mg/kg/day. Children born to mothers treated with streptomycin injections at therapeutically-relevant dose levels have sometimes had hearing loss; no teratogenic effects have been attributed to streptomycin treatment. Because the dose selected for risk assessment is much lower than the injected dose at which toxicity occurs in humans, and at the levels of exposure anticipated due to pesticidal uses, there is no indication of neurotoxicity or susceptibility, and there are no residual concerns, the FQPA safety factor was reduced to 1x.

4.4.1 Completeness of the Toxicology Database

All toxicological data requirements were waived in the previous streptomycin risk assessments (D310386 and D394862) because of the extensive database in humans and animals that exists from streptomycin drug use. Additionally, a more recent assessment of the database by the Hazard and Science Policy Council (HASPOC; TXR# 0056935, dated April 29, 2014) concluded that, based on a weight of the evidence approach, additional toxicity studies are not required for streptomycin.

4.4.2 Evidence of Neurotoxicity

The extensive database in humans and animals does not demonstrate any potential for streptomycin to cause either peripheral or central nervous system toxicity at exposure levels expected from the proposed uses.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

There is no direct evidence of sensitivity/susceptibility in the developing or young animal. No teratogenic effects were observed in the rabbit. As noted above, children born to mothers treated with streptomycin injections have sometimes had hearing loss, but no teratogenic effects have been attributed to streptomycin treatment. Chosen points of departure are expected to be protective of any possible hearing loss.

4.4.4 Residual Uncertainty in the Exposure Database

EPA is confident that the aggregate risk from exposure to streptomycin in food, drinking water, and residential pathways will not be underestimated. The exposure database for streptomycin is adequate for dietary exposure and risk assessment purposes. The chronic dietary food exposure assessment is conservative, as tolerance level residues based on pesticidal uses, tolerances established in the 21 CFR § 556.610 for livestock commodities in support the use of streptomycin as an animal drug, and 100% of crop treated assumptions were used. Also, conservative modeled estimated drinking water concentrations (EDWC) were incorporated in the dietary assessment. This EDWC was calculated with the Pesticide Root Zone Model – Groundwater for the most conservative application use pattern on apples and pears, and the most vulnerable groundwater scenario. The residential exposure assessment is based on the updated 2012 Residential SOPs employing surrogate study data and including conservative exposure assumptions. The Residential SOPs are based upon reasonable “worst-case” assumptions and are not expected to underestimate risk.

4.5 Toxicity Endpoint and Point of Departure Selections

4.5.1 Dose-Response Assessment

All toxicological data requirements were waived for streptomycin. The database provides sufficient information for selection of endpoints when the extensive human literature for streptomycin is included. The 2-year rat feeding study was used by FDA; the World Health Organization (WHO); and by EPA in the streptomycin Registration Eligibility Decision (RED), in previous risk assessments and in this risk assessment to determine the chronic dietary reference dose (RfD), the incidental oral point of departure (POD), and the inhalation POD. The 2-year rat feeding study is also used by FDA and WHO for regulating animal drug uses of streptomycin in meat. Because oral absorption of aminoglycosides related to streptomycin is less than 1% and the skin has a protective barrier role compared to the lining of the GI tract, dermal absorption should be much less than that by the oral route. Consequently, toxicity by the dermal route at environmental concentrations is not expected. Therefore, quantitation of risk following dermal exposure was not required. The points of departure, uncertainty factors, and toxicity endpoints are presented in the following tables.

4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

When there are potential occupational and residential exposures to a pesticide, the risk assessment must address exposures from three major routes (oral, dermal, and inhalation) and determine whether the individual exposures can be combined if they have the same toxicological effects. PODs for the oral and inhalation routes are all based on reduced body weight in males. As a result, exposure from these routes can be combined. An endpoint to assess dermal exposure was not established due to the minimal dermal adsorption expected for streptomycin.

4.5.3 Cancer Classification and Risk Assessment Recommendation

There is not enough information to classify the carcinogenic potential of streptomycin since guideline carcinogenicity studies are not available. The toxicological data requirements for streptomycin have been waived due to the extensive human database from streptomycin drug use. However, a 2 year rat carcinogenicity study, used by FDA and the WHO (to set tolerances for animal drug residues), is available for streptomycin and did not demonstrate evidence of carcinogenicity (although limited histopathology was reported). Also, a literature search for streptomycin toxicity in animals and humans did not result in data with evidence of carcinogenicity. A mouse carcinogenicity study is not available for streptomycin.

4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.4 Summary of Toxicological Doses and Endpoints for Streptomycin for Use in Dietary and Non-Occupational Human Health Risk Assessments.				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (All Populations)	Toxicity from single-dose exposure not identified.			
Chronic Dietary (All Populations)	NOAEL= 5 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Chronic RfD = 0.05 mg/kg/day cPAD = 0.05 mg/kg/day	2-year feeding study in rats LOAEL = 10 mg/kg/day based on reduced body weight in males.
Incidental Oral (Short- and Intermediate-Term)	NOAEL= 5 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Residential LOC for MOE = 100	2-year feeding study in rats LOAEL = 10 mg/kg/day based on reduced body weight in males.
Short-term oral (adult)	NOAEL= 5 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Residential LOC for MOE = 100	2-year feeding study in rats LOAEL = 10 mg/kg/day based on reduced body weight in males.
Dermal (Short- and Intermediate-Term)	Not required because of minimal dermal absorption.			
Inhalation (Short- and Intermediate-Term)	NOAEL= 5 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Residential LOC for MOE = 100	2-year feeding study in rats LOAEL = 10 mg/kg/day based on reduced body weight in males.
Cancer (oral, dermal, inhalation)	Classification: There is not enough information to classify the carcinogenic potential of streptomycin since guideline carcinogenicity studies are not available. The toxicological data requirements for streptomycin have been waived due to the extensive human database from streptomycin drug use. However, a 2 year rat carcinogenicity study, used by FDA and the World Health Organization (to set tolerances for animal drug residues), is available for streptomycin and did not demonstrate evidence of carcinogenicity (although limited histopathology was reported). Also, a literature search for streptomycin toxicity in animals and humans did not result in data with evidence of carcinogenicity. A mouse carcinogenicity study is not available for streptomycin.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern.

Table 4.2.2 Summary of Toxicological Doses and Endpoints for Streptomycin for Use in Occupational Human Health Risk Assessments.				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short-(1-30 days) and Intermediate-(1-6 months) Terms	Not required because of minimal dermal absorption.			
Inhalation Short-(1-30 days) and Intermediate-(1-6 months) Terms	NOAEL= 5 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Residential LOC for MOE = 100	2-year feeding study in rats LOAEL = 10 mg/kg/day based on reduced body weight in males.
Cancer (oral, dermal, inhalation)	Classification: There is not enough information to classify the carcinogenic potential of streptomycin since guideline carcinogenicity studies are not available. The toxicological data requirements for streptomycin have been waived due to the extensive human database from streptomycin drug use. However, a 2 year rat carcinogenicity study, used by FDA and the World Health Organization (to set tolerances for animal drug residues), is available for streptomycin and did not demonstrate evidence of carcinogenicity (although limited histopathology was reported). Also, a literature search for streptomycin toxicity in animals and humans did not result in data with evidence of carcinogenicity. A mouse carcinogenicity study is not available for streptomycin.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern.

4.6 Qualitative Assessment of Antimicrobial Resistance

A qualitative assessment of bacterial resistance to streptomycin in food commodities will be made by the Registration Division to document the potential health consequence of streptomycin with regards to the emergence of antibiotic resistant bacteria.

5.0 Dietary Exposure and Risk Assessment

5.1 Residues of Concern Summary and Rationale

The 1988 Registration Standard determined that because streptomycin is widely used as a human and animal drug, metabolism data are not needed to support its limited use as a fungicide on crops. Therefore, the residue of concern for plants and livestock is parent streptomycin only (Table 4.2).

Table 5.1. Summary of Metabolites and Degradates to be Included in the Risk Assessment and Tolerance Expression[1]			
Matrix		Residues Included in Risk Assessment	Residues Included in Tolerance Expression
Plants	Primary Crop	Streptomycin	Streptomycin
	Rotational Crop		
Livestock	Ruminant		
	Poultry		
Drinking Water			Not Applicable

[1] 2005 TRED

5.2 Food Residue Profile

Crop field trial data was submitted to support the registration for the use of streptomycin on tomato and grapefruit. Residues of streptomycin on grapefruit and tomato ranged from <0.01 to 0.0855 ppm and 0.0162 to 0.413 ppm, respectively. Tolerances based on residues of streptomycin are recommended at 0.15 ppm for grapefruit and 0.50 ppm for tomato. Concentration of residues of streptomycin upon processing may occur; therefore, tolerances for processed commodities of grapefruit dried pulp (0.3 ppm) and tomato paste (1.2 ppm) are recommended. A crop group conversion from pome fruit group 11 to pome fruit group 11-10 is recommended as well. Currently, tolerances ranging from 0.25 to 0.50 ppm are established in 40 CFR 180.245 to support uses of streptomycin on celery, pepper, potato, dry bean seed, and succulent bean. Moreover, there is a potential exposure to residues of streptomycin on livestock commodities. Tolerances are established in the 21 CFR § 556.610 to support the use of streptomycin as an animal drug. These tolerances are based on residues of streptomycin in uncooked, edible tissues of chickens, swine, and calves at 2.0 ppm in kidney and 0.5 ppm in other tissues.

5.3 Water Residue Profile

The drinking water residues used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED) in the following memorandum: "Revised Drinking Water Assessment for the Proposed New Use of Streptomycin Sulfate on Grapefruit and Tomatoes" (A. Shelby, D427238, 05/21/2015). Exposures from surface water and groundwater have been modeled by considering currently registered and proposed uses. Estimated drinking water concentrations (EDWCs) from ground water exposures were higher than for surface water exposures and are thus the risk driver for streptomycin. EDWCs calculated with PRZM-GW (Version 1.07) for the highest use rate of streptomycin (apples and pears) with the most vulnerable groundwater scenario (Wisconsin Sands) were recommended by EFED for use in HED dietary assessment. These values were 932 ppb for acute exposure (peak) and 760 ppb for chronic exposure (post breakthrough average).

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

The chronic dietary exposure and risk analysis used tolerance-level residues for all the registered uses and proposed new uses. DEEM™ default processing factors were used for all processed commodities, except grapefruit juice and tomato puree where concentration is not expected (i.e. empirical processing factors <1x), and tomato paste since a tolerance is being recommended. Tolerances for livestock commodities resulting from the use of streptomycin as an animal drug were included as well.

5.4.2 Percent Crop Treated Used in Dietary Assessment

For all commodities it was assumed that 100% of the crop was treated (i.e. %CT).

5.4.3 Acute Dietary Risk Assessment

An acute dietary exposure analysis was not conducted for streptomycin because no appropriate endpoint attributable to a single exposure was identified for the general U.S. population or any population subgroup.

5.4.4 Chronic Dietary Risk Assessment

An unrefined chronic dietary assessment was performed for streptomycin. The estimated exposure (food and water) to the U.S. population from the existing and proposed new uses of streptomycin resulted in an estimated risk equivalent to 41% of the cPAD. The most highly exposed subpopulation was all infants (<1 year old) with an estimated exposure equivalent to 91% of the cPAD. An analysis of the chronic dietary risk considering exposure to food only results in risks ≤ 21% of the cPAD for the general population and all population subgroups; therefore, drinking water is the highest contributor to dietary exposure to streptomycin. If needed in the future, the drinking water exposure may be further refined (A. Shelby, D427238, 21-MAY-2015).

5.4.5 Cancer Dietary Risk Assessment

A cancer dietary exposure and risk assessment was not conducted since streptomycin is not likely to be carcinogenic to humans.

5.4.6 Summary Table

The results of the chronic dietary exposure analyses are reported in Table 5.4.6. Risks are below the level of concern of (< 100%) of the cPAD.

Table 5.4.6. Summary of Chronic Dietary Exposure and Risk for Streptomycin.				
Population Subgroup	Food and Drinking Water		Food Only	
	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.020637	41	0.010507	21
All Infants (<1 year old)	0.045572	**91**	0.041085	82
Children 1-2 years old	0.040179	80	0.025412	51
Children 3-5 years old	0.032991	66	0.019561	39
Children 6-12 years old	0.020801	42	0.010510	21
Youth 13-19 years old	0.015854	32	0.006746	14
Adults 20-49 years old	0.019463	39	0.008628	17
Adults 50-99 years old	0.019125	38	0.010280	21
Females 13-49 years old	0.019264	38	0.008093	16

[1] The subpopulation(s) with the highest risk estimates is in bold.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are existing residential uses on gardens and trees that were previously assessed using HED's 2012 Residential SOPs[2] along with policy changes for body weight assumptions (Memo, K. Lowe, D426601, 09-FEB-2016). Residential handler exposures are anticipated from registered use on ornamentals. Residential post-application exposures were not assessed, because no quantitative dermal assessment is required for streptomycin. Further, non-dietary ingestion and inhalation post-application exposure is assumed to be negligible following applications to ornamentals (gardens and trees). A summary of the residential handler scenarios previously assessed is provided below. For all handler scenarios considered, estimated inhalation risks were not of concern (i.e., MOEs ≥ LOC of 100): the lowest calculated MOE was 86,000 (see Table 6.0).

The labels that were assessed for residential uses were identified as such due to the use sites, equipment, and in particular, their lack of personal protective equipment (PPE). HED notes that there are registered streptomycin products that are intended for use in residential sites (e.g., EPA Reg. Nos. 64864-43 and 80990-3), but labels require certain clothing and/or PPE to be worn – a long sleeve shirt, pants, gloves, and a respirator. Standard HED assumptions for residential/consumer applicator specific assessments, such as wearing shorts and a t-shirt without PPE like chemical-resistant gloves or respirators, would represent non-compliance with current streptomycin products; therefore, a residential handler assessment has only been conducted for those labels registered for residential use sites that do not require PPE. If products containing streptomycin are meant to be marketed towards and performed by consumers/homeowners in residential sites, HED recommends that label requirements for clothing and/or PPE be reevaluated or separate consumer-specific labels be developed and a separate residential handler assessment be conducted to evaluate such products.

[2] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

Table 6.0. Residential Handler Non-cancer Exposure and Risk Estimates for Streptomycin.						
Exposure Scenario	Level of Concern	Inhalation Unit Exposure (mg/lb ai)	Maximum Application Rate[1] (lb ai/gallon)	Amount Handled Daily (gal)[2]	Inhalation	
					Dose (mg/kg/day)[3]	MOE[4]
Mixer/Loader/Applicator						
Manually-pressurized handwand, Wettable Powder, Gardens/Trees	100	1.1	0.00085	5	0.000058	86,000
Hose-end sprayer, Wettable Powder, Gardens/Trees	100	0.0014	0.00085	11	0.00000016	31,000,000
Backpack, Wettable Powder, Gardens/Trees	100	1.1	0.00085	5	0.000058	86,000
Sprinkler Can, Wettable Powder, Gardens/Trees	100	0.0014	0.00085	5	0.000000074	67,000,000

1 Based on registered uses (e.g., EPA Reg. # 7404-311).
2 Based on HED's 2012 Residential SOPs (http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/gal) × Amount Handled (A/day or gallons/day) ÷ BW (80 kg).
4 Inhalation MOE = Inhalation NOAEL (5 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

In accordance with 40 CFR 158, the following data are required for all occupational or residential pesticide uses: (1) dislodgeable foliar residue (DFR) data are required for all occupational (e.g., crop, nursery, greenhouse use sites) or residential (e.g., ornamental and vegetable gardens, pick your own farms, retail tree farms) uses that could result in post-application exposure to foliage, and (2) turf transferable residue (TTR) data are required for all occupational (e.g., sod farms, golf courses, parks, and recreational areas) or residential turf uses that could result in post-application exposure to turf. Since there is no dermal hazard identified for streptomycin, and residential post-application incidental oral exposures are not expected from the registered uses, DFR data are not required for streptomycin at this time. Additionally, there are no registered uses that would trigger the requirement for TTR data.

6.1 Residential Risk Estimates for Use in Aggregate Assessment

Table 6.1 reflects the residential risk estimates that are recommended for use in the aggregate assessment for streptomycin. Since there are no residential exposures quantified for children, only recommendations for the adult aggregate are presented below.

- The recommended residential exposure for use in the adult aggregate assessment is inhalation exposure from applications to gardens/trees via backpack/handwand sprayer.

Table 6.1. Recommendations for the Residential Exposures for the Streptomycin Aggregate Assessment.									
Lifestage	Exposure Scenario	Dose (mg/kg/day)[1]				MOE[2]			
		Dermal	Inhalation	Oral	Total	Dermal	Inhalation	Oral	Total
Adult	M/L/A for Backpack application of a Wettable Powder to Gardens/Trees	NA	0.000058	NA	**0.000058**	NA	86,000	NA	**86,000**

1 Dose = the highest dose for each applicable lifestage of all residential scenarios assessed. Total = dermal + inhalation + incidental oral (where applicable).
2 MOE = the MOEs associated with the highest residential doses. Total = 1 ÷ (1/Dermal MOE) + (1/Inhalation MOE) + (1/Incidental Oral MOE), where applicable.

6.2 Residential Bystander Post-application Inhalation Exposure

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219).

During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for streptomycin.

6.3 Non-Occupational Exposure and Risk Estimates Resulting from Spray Drift

A quantitative assessment of exposure and risk resulting from spray drift was previously conducted for streptomycin (Memo, K. Lowe, 09-FEB-2016, D426601), which resulted in no incidental oral risk estimates of concern for children (1 < 2 year old) [i.e., all margins of exposure (MOEs) ≥ 100] at the field edge for the maximum registered agricultural rate of 0.5 lb streptomycin/A for airblast applications. Since the rate assessed previously for spray drift resulting from airblast applications is higher than the proposed rate, this previous assessment is protective of the proposed Section 3 use. A summary of the spray drift risk estimates is provided in Table 6.3.1.

Table 6.3.1. Non-occupational Risk Estimates Resulting from Spray Drift for Streptomycin.

Crop/Rate Group	Spray Type/ Nozzle Configuration	Application Rate (lb ai/A)	Estimated TTR_t (ug/cm^2)[a]	HtM MOE at Field Edge
Aerial	Fine to Medium	0.5	0.056	2,600
Airblast	Sparse			4,600
Groundboom	High Boom Very fine to Fine	0.34	0.038	5,200

a. Default TTR = Application Rate × F × $(1\text{-}D)^t$ × 4.54E8 µg/lb × 2.47E-8 $acre/cm^2$.

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

A short-term aggregate assessment was conducted because the residential use under consideration is considered to have short-term exposure. Short-term aggregate assessments include exposures that will occur from one to thirty days. Aggregate exposure for streptomycin

included background dietary (food and water) and inhalation exposures. The adult population group with the highest dietary exposure (i.e. Adults 20-49 years old) and the residential scenario resulting in highest exposure (i.e. handler using handwand/backpack), were used to assess aggregate exposure. The dermal route was not included, because no dermal hazard exists for this chemical. The aggregate risk assessment for adults are not of concern (i.e. MOEs ≥ LOC of 100), see Table 7.0. With respect to children, since the residential exposure is not quantitatively assessed, the child aggregate assessment includes only contributions from food and drinking water, and is presented in Section 5.

Table 7.0 Short-Term Term Aggregate Risk Estimates.

Population	Short- or Intermediate-Term Scenario						
	NOAEL mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food and Water Exposure mg/kg/day[3]	Residential Exposure mg/kg/day[4]	Total Exposure mg/kg/day[5]	Aggregate MOE (food, water, and residential)[6]
Adult	5	100	0.05	0.019463	0.000058	0.019521	260

[1] Inter- and intra- species uncertainty factors totaling 100.
[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC
[3] Dietary exposure from adults 20-49 years, see table 5.4.
[4] Residential Exposure = Inhalation Exposure, see Table 6.1.
[5] Total Exposure = Avg Food & Water Exposure + Residential Exposure.
[6] Aggregate MOE = [NOAEL / (Avg Food & Water Exposure + Residential Exposure)]

8.0 Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to streptomycin and any other substances, and streptomycin does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action; therefore, EPA has not assumed that streptomycin has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Characterization

9.1 Short-/Intermediate-Term Handler Risk

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications, and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the proposed uses.

The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

- Mixing/loading and applying wettable powder via airblast equipment to orchards,
- Mixing/loading and applying wettable powder via groundboom equipment to field crops, and
- Mixing/loading and applying with handgun for greenhouse crops.

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed below on an individual basis.

Application Rate: The application rates for the proposed uses are described in Table 3.3.

Unit Exposures: It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include PHED 1.1, the AHETF database, the Outdoor Residential Exposure Task Force (ORETF) database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[3]", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[4].

Area Treated or Amount Handled:

- Airblast applications to orchards: 40 acres
- Groundboom applications to field crops: 80 acres
- Handgun applications: 1000 gallons

Exposure Duration: HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. Exposure duration is determined by many things, including the exposed population, the use site, the pest pressure triggering the use of the pesticide, and the cultural practices surrounding that use site. For most agricultural uses, it is reasonable to believe that occupational handlers will not apply the same chemical every day for more than a one-month time frame; however, there may be a large agribusiness and/or commercial applicators who may apply a product over a period of weeks (e.g., completing multiple applications for multiple clients within a region). For streptomycin, based on the proposed use, short- and intermediate-term exposures are expected.

Mitigation/Personal Protective Equipment: Estimates of dermal and inhalation exposure were calculated for various levels of PPE. Results are presented for "baseline," defined as a single layer of clothing consisting of a long sleeved shirt, long pants, shoes plus socks, no protective gloves, and no respirator, as well as baseline with various levels of PPE as necessary (e.g., gloves, respirator, etc.). The streptomycin product label (EPA Reg. No. 80990-4) directs mixers, loaders, applicators and other handlers to wear long-sleeved shirt, long pants, chemical-resistant

[3] Available: http://www.epa.gov/opp00001/science/handler-exposure-table.pdf
[4] Available: http://www.epa.gov/pesticides/science/handler-exposure-data.html

gloves, shoes plus socks, and a dust/mist respirator; therefore, results are also presented for use of a PF5 respirator.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

All occupational handler MOEs are greater than the LOC of 100 and are thus not of concern. MOEs range from 450 to 87,000 at baseline PPE. MOEs range from 2,300 to 430,000 with the label-required PPE of the dust/mist respirator. As dermal risk is not quantitatively assessed, routes of exposure are not combined.

Table 9.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Streptomycin.

Exposure Scenario	Crop or Target	Level of Concern	Inhalation Unit Exposure (µg/lb ai)[1]		Maximum Application Rate (lb strep/acre)[2]	Area Treated or Amount Handled Daily (acres)[3]	Inhalation - Baseline		Inhalation – PF5 Respirator	
			Mitigation - Baseline	Mitigation – PF5 Respirator			Dose (mg/kg/day)[4]	MOE[5]	Dose (mg/kg/day)[4]	MOE[5]
Mixer/Loader										
WP, Airblast	Grapefruit	100	43	8.6	0.51	40	0.011	450	0.00219	2,300
WP, Groundboom	Tomato				0.17	80	0.00731	680	0.00146	3,400
Applicator										
Airblast	Grapefruit	100	4.71	0.942	0.51	40	0.0012	4,200	0.00024	21,000
Groundboom	Tomato		0.34	0.068	0.17	80	0.0000578	87,000	0.0000116	430,000
Mixer/Loader/Applicator										
WP, Mechanically-pressurized handgun	Greenhouse Tomato	100	3.9	0.78	0.0017 lb ai/gallon	1000 gallons	0.0000829	60,000	0.0000166	300,000

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (March 2013); Level of mitigation: Baseline, PF5 Respirator.
2 Based on proposed label: Firewall 17WP (EPA Reg. No. 80990-4). Note that the application rate in terms of streptomycin were calculated based on the labeled rates, which are in term of the end-use product and the active ingredient, streptomycin sulfate.
3 Exposure Science Advisory Council Policy #9.1.
4 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ BW (80 kg).
5 Inhalation MOE = Inhalation NOAEL (5 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

9.2 Short-/Intermediate- Term/ Post-Application Risk

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

9.2.1 Dermal Post-application Risk

As there is no dermal hazard identified for streptomycin, quantification of occupational post-application dermal exposure/risk is not required.

In accordance with 40 CFR § 158, dislodgeable foliar residue (DFR) data are required for all occupational (e.g., crop, nursery, greenhouse use sites) or residential (e.g., ornamental and vegetable gardens, pick your own farms, retail tree farms) uses that could result in post-application exposure to foliage. However, since there is no dermal hazard identified for streptomycin, DFR data are not required for streptomycin at this time.

Restricted Entry Interval

Since a quantitative dermal post-application assessment was not required, the restricted entry interval (REI) specified on the proposed label is based on the acute toxicity of streptomycin. Under 40 CFR 156.208 (c) (2) (iii), ai's classified as Acute III or IV for acute dermal, eye irritation and primary skin irritation, or acute oral toxicity if lacking the dermal toxicity, are assigned a 12-hour REI. Therefore, the [156 subpart K] Worker Protection Statement interim REI of 12 hours is adequate to protect agricultural workers from post-application exposures to streptomycin.

9.2.2 Inhalation Post-application Risk

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for streptomycin.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the agency's risk assessments.

Although a quantitative occupational post-application inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for occupational/commercial handlers. Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than post-application exposure. Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios.

Furthermore, inhalation exposure during dusty mechanical activities such as shaking and mechanical harvesting is another potential source of post-application inhalation exposure. However, the airblast applicator scenario is believed to represent a reasonable worst case surrogate estimate of post-application inhalation exposure during these dusty mechanical harvesting activities. The non-cancer inhalation risk estimate for commercial airblast application is not of concern (i.e., MOE > 100).

The Worker Protection Standard for Agricultural Pesticides contains requirements for protecting workers from inhalation exposures during and after greenhouse applications through the use of ventilation requirements.[40 CFR 170.110, (3) (Restrictions associated with pesticide applications)].

10.0 References

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Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.500) for food use for Streptomycin are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Toxicology data requirements were waived because of the extensive human database for streptomycin from many years of drug use (HASPOC; TXR# 0056935, dated April 29, 2014).

Study		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	waived
870.1200	Acute Dermal Toxicity	yes	waived
870.1300	Acute Inhalation Toxicity	yes	waived
870.2400	Acute Eye Irritation	yes	waived
870.2500	Acute Dermal Irritation	yes	waived
870.2600	Skin Sensitization	yes	waived
870.3100	90-Day Oral Toxicity in Rodents	Yes	waived
870.3150	90-Day Oral Toxicity in Nonrodents	Yes	waived
870.3200	21/28-Day Dermal Toxicity	Yes	waived
870.3250	90-Day Dermal Toxicity	Yes	waived
870.3465	90-Day Inhalation Toxicity	CR	--
870.3700a	Prenatal Developmental Toxicity (rodent)	Yes	waived
870.3700b	Prenatal Developmental Toxicity (nonrodent)	Yes	waived
870.3800	Reproduction and Fertility Effects	Yes	waived
870.4100a	Chronic Toxicity (rodent)	Yes	waived
870.4100b	Chronic Toxicity (nonrodent)	Yes	waived
870.4200a	Carcinogenicity (rat)	Yes	waived
870.4200b	Carcinogenicity (mouse)	Yes	waived
870.4300	Combined Chronic Toxicity/Carcinogenicity	--	--
870.5100	Mutagenicity—Bacterial Reverse Mutation Test	Yes	waived
870.5300	Mutagenicity—Mammalian Cell Gene Mutation Test	Yes	waived
870.5xxx	Mutagenicity—Structural Chromosomal Aberrations	Yes	waived
870.5xxx	Mutagenicity—Other Genotoxic Effects	--	--
870.6200a	Acute Neurotoxicity Screening Battery (rat)	Yes	waived
870.6200b	90-Day Neurotoxicity Screening Battery (rat)	Yes	waived
870.6300	Developmental Neurotoxicity	CR	--
870.7485	Metabolism and Pharmacokinetics	Yes	waived
870.7600	Dermal Penetration	CR	--
870.7800	Immunotoxicity	Yes	waived

Appendix B. Physical/Chemical Properties

Table B1. Physico-Chemical Properties		
Parameter	**Value**	**Reference**
Molecular weight (g/mole)	1467.48 (sulfate salt)	D176743, 6/19/92, C. Swartz
Melting point/range (°C)	168 °C	D176743, 6/19/92, C. Swartz
pH	5.5 (1g sample/ 5 ml water)	D176743, 6/19/92, C. Swartz
Density (g/cm^3)	1.78	D176743, 6/19/92, C. Swartz
Water solubility (at 28°C)	>20 mg/ml	*Merck* 12, 8983
Solvent solubility	Soluble in methanol, ethanol, isopropanol, carbon tetrachloride, and ether	*Merck* 12, 8983
Dissociation constant (pK_a)	7.97	D187344, 5/4/93, C. Swartz
Octanol/water partition coefficient Log(K_{OW})	Waived	

Appendix C. International Residue Limits Table

Streptomycin (PC Code 006306)

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[2]	Codex
40 CFR 180.245: (a) General. (1) Tolerances are established for residues of the fungicide streptomycin		None		None
Commodity[1]	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[2]	Codex
Grapefruit	0.15			
Grapefruit, dry fruit	0.3			
Fruit, pome, group 11-10	0.25			
Tomato	0.5			
Completed: M. Negussie; 10/08/2014				

[1] Includes only commodities of interest for this action. Tolerance values should be the HED recommendations and not those proposed by the applicant.

[2] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

Appendix D. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from PHED 1.1; the AHETF database; and the Outdoor Residential Exposure Task Force (ORETF) database, are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[5].

[5] http://www.epa.gov/pesticides/science/handler-exposure-data.html and http://www.epa.gov/pesticides/science/post-app-exposure-data.html